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MATERNAL HEALTH

New drug regimens for HIV in pregnancy and a national strategic plan to manage HIV: A South African perspective

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ABSTRACT

In South Africa, new drug regimens (WHO treatment Option B) used to manage HIV infection in pregnancy and the national strategic plan on HIV have resulted in improved health outcomes. Among these outcomes are reductions in the following: mother-to-child transmission (MTCT) of HIV to 2.4%; maternal deaths attributable to HIV; and adverse reactions due to antiretroviral therapy (ART). The present article describes these new drug regimens and the national strategic HIV management plan, as well as their challenges and the implications of improved health outcomes. Such outcomes imply that further decreases in MTCT of HIV, and HIV attributable maternal deaths are possible if potential challenges are addressed and treatment option B+ offered. A confidential enquiry into each case of MTCT is advocated to reduce vertical transmission rates to zero levels.

1. Introduction

In 2012, approximately 35.3 (32.2–38.8) million people, 70% of whom were women, were living with HIV infection worldwide; Sub-Saharan Africa accounts for 71% of this figure [1]. In the same year, an estimated 6.1 million people were living in South Africa with HIV infection; this constitutes an overall prevalence rate of 17.9%, making South Africa the country with the highest number of people infected with this retroviral disease [2]. This has translated to a high burden of HIV infection among pregnant women. To lessen this burden, new drug regimens and strategies have been introduced internationally and across nations. For instance, in 2001 the United Nations developed the four-pronged framework for the prevention of mother-to-child transmission (MTCT) of HIV. The components of this framework are primary prevention of HIV infection; prevention of unplanned pregnancies; prevention of MTCT; and the provision of appropriate care, treatment, and support to HIV-infected mothers, their children, and families [3]. In an attempt to improve care, South Africa has developed management guidelines and health policies that have repeatedly been revised based on emerging evidence and the resources available to the country.

The new antiretroviral drug regimens [4] and national strategic plan [5] for the management of HIV in pregnancy in South Africa are leading to improved health outcomes. Notably, the national prevalence of HIV in pregnancy has declined from 30% in 2010 to 29.5% in 2012 [2]. Data on the number of HIV-exposed infants who tested polymerase chain reaction (PCR) positive at approximately two months of age show that the rate of MTCT has also declined from 9.6% in 2008 to 4.4% in 2010 [6] and to 2.4% in 2013 [7]. The 2013 interim Saving Mothers report has shown that the institutional maternal mortality ratio in South Africa has decreased from 176.2 per 100 000 live births in 2008−2010 to 146.7 per 100 000 live births in 2012. The decline in maternal deaths is attributable to a reduction in the number of deaths resulting from nonpregnancy-related infections, primarily HIV [8]. Similarly, maternal deaths resulting from an adverse reaction to antiretroviral therapy (ART)—nevirapine (NVP) in particular—have also declined [9].

The present article describes South Africa's new drug regimen and national strategic plan used for the management of HIV in pregnancy, their outcomes and challenges, and the implications of further reductions in MTCT rates.

2. WHO treatment options for prevention of mother-to-child transmission of HIV

Different ART options have been used for prevention of mother-to-child transmission (PMTCT) of HIV [10]. In 2012, WHO introduced three management categories: option A, option B, and option B+ [11].

2.1. Option A

Triple antiretroviral drugs (ARVs) are started following diagnosis and continued for life (life-long) if the pregnant woman has a CD4 count less than or equal to 350 cells/mm^3. Pregnant women with a CD4 count greater than 350 cells/mm^3 receive zidovudine (AZT) from

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14 weeks of gestation in the prenatal period; single-dose NVP, AZT, and lamivudine (3TC) during labor; and AZT plus 3TC for seven days postpartum. The infants of these mothers receive daily NVP for an extra week following cessation of breastfeeding, or for 4−6 weeks (if not being breastfed or if the mother is on life-long ARVs).

2.2. Option B

Life-long triple ARVs are started following diagnosis in women with CD4 less than or equal to 350 cells/mm^3. In women with CD4 greater than 350 cells/mm^3, triple ARVs are commenced from 14 weeks of gestation throughout the prenatal period and stopped after childbirth (if not breastfeeding), or continued up to one week after cessation of breastfeeding. The infants of these mothers receive daily NVP or AZT until they are 4−6 months old irrespective of infant feeding practices.

2.3. Option B+

Every pregnant woman diagnosed with HIV infection is commenced on life-long triple ARVs irrespective of CD4 count. The infants of these mothers receive daily NVP or AZT until they are 4−6 months old regardless of infant feeding practices.

2.4. Rational behind the different treatment options

Treatment options A, B, and B+ were suggested by WHO for the following reasons: the global plan to eliminate new cases of HIV infection in children by 2015 and the need to keep infected mothers alive; attempt to reduce HIV transmission among discordant couples; operational challenges associated with option A and option B; some countries proposing their wish to adopt option B+; initiative to simplify ARV regimen to be exactly the same as the national first-line ART for nonpregnant adults and avoid the need to unnecessarily change ARV during a pregnancy; data suggesting that efavirenz is safe in pregnancy; and increasing affordability of ARVs [11]. It has also been established that NVP causes adverse reactions, especially hepatotoxicity, at baseline CD4 counts of greater than 250 cells/mm^3 and greater than 400 cells/mm^3 in women [12] and men [13], respectively. In addition, an increasing incidence of cases of hepatic failure and Stevens-Johnson syndrome has been detected in pregnant patients on NVP [9]. The availability of a single pill containing a fixed-dose combination of tenofovir, lamivudine, and efavirenz has simplified the ARV regimen and efficiency [11].

2.5. Probability of vertical HIV transmission with the use of different treatment options

There is a scarcity of studies that assess transmission probabilities when all aspects of each WHO treatment option are addressed in the targeted population [14,15]. However, use of mathematical models, such as Spectrum, shows the following MTCT probabilities: single-dose NVP, 9.4%−12.1%; WHO 2006 dual therapy, 2.3%−5.3%; option A, 2%; option B, 0.9%−2.9%; and option B+, less than 2% [15].

3. New PMTCT drug regimens in South Africa

The use of ARVs for PMTCT was first introduced in South Africa as national policy in 2002. The regimen involved the administration of single-dose NVP to both the mother (during labor) and her newborn (after delivery). Since then, the PMTCT program was modified in 2005 and 2008, and option A was introduced in 2010 [16]. Thereafter, option B was introduced in 2013 and constitutes current practice at the time of writing the present article [4]. The current drug regimen in South Africa is similar to WHO option B with the exception that South African guidelines state that pregnant women with CD4 greater than 350 cell/mm^3 are initiated on ART during the first prenatal visit, even before 14 weeks of gestation. This South African drug regimen is satisfactory (as option B) given the acceptable safety profile of efavirenz in pregnancy, and that the longer the duration of ART before delivery then the less chance of MTCT of HIV [17]. Table 1 provides a summary of the ARV regimen used for PMTCT in South Africa. Further details on the drug regimens used for PMTCT in South Africa are free to view online [4]. The purpose of the South African PMTCT guidelines is to ensure that every possible preventable MTCT, using option B, is achieved.

4. South African national strategic plan on HIV

Strategic planning may be defined as "the systematic and organized process whereby an organization creates a document indicating the way it plans to progress from its current situation to the desired future situation" [18]. Several approaches have been used to develop strategic planning. A common classical method involves the following five processes: (1) establishing mission, vision, and values; (2) strategy formulation involving an analysis of internal and external environments, SWOT (strengths, weaknesses, opportunities, and threats) matrix, strategic alternatives, areas and objectives; (3) operational planning; (4) evaluation of results; and (5) strategy reformulation [18].

Table 1
Summary of antiretroviral therapy approved for prevention of mother-to-child transmission of HIV in South Africa in 2013.

Recipient	Antiretroviral therapy
Mother	All pregnant women except those already known to be HIV infected undergo Provider Initiated Counselling and Testing during the first prenatal visit. HIV-infected women are then managed as outlined below. Women who are HIV infected are started on fixed-dose combination (FDC) of TDF, FTC/3TC, EFV the same day (in the absence of active psychiatric or renal disorder) and reviewed in one week. Women with contraindication to FDC (such as active psychiatric or renal disorder) are started on daily AZT (300 mg) the same day as long as the hemoglobin is greater than 7 g/dL. Following a review in one week, they are placed on appropriate regimen. Women on FDC with a baseline CD4 count less than or equal to 350 cell/mm^3 or WHO clinical stage 3/4 disease, the treatment is continued life-long. Women on FDC with a baseline CD4 count greater than 350 cell/mm^3 or WHO clinical stage 1/2 disease, the treatment is continued throughout the prenatal and intrapartum period until one week after complete cessation of breastfeeding. Women having renal impairment with CD4 less than or equal to 350 cells/mm^3 or WHO stage 3/4 are later commenced on FDC unless the serum creatinine is greater than 85 μmol/L, in which case they receive a renal-friendly regimen, AZT + 3TC + EFV for life (but ABC or d4T is used if AZT is contraindicated). With a CD4 count greater than 350 cell/mm^3 or WHO clinical stage 1/2 disease, the patient receives daily AZT prenatally, AZT 3 hourly plus sd NVP and sd TDF/FTC intrapartum. Women having psychiatric disorder with CD4 less than or equal to 350 cells/mm^3 or WHO stage 3/4 are commenced on life-long TDF + FTC + NVP (or LPV/RTV if CD4 greater than 250 cells/mm^3). With a CD4 count greater than 350 cell/mm^3 or WHO clinical stage 1/2 disease, the patient receives: prenatally AZT daily; intrapartum AZT 3 hourly plus sd NVP and sd TDF/FTC. Women who test HIV positive for the first time in labor are given sd NVP plus AZT 3 hourly and sd TDF + FTC.
Infants	Infants born to HIV-infected mothers receive daily NVP for at least six weeks or until one week after cessation of breastfeeding.[a]

Abbreviations: AZT, Zidovudine; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; LPV/RTV, lopinavir/ritonavir; NVP, nevirapine; sd, single dose; TDF, tenofovir; 3TC, lamivudine.
[a] Mixed feeding is not a recommended infant feeding option.

In South Africa, the national strategic plan on HIV, sexually transmitted infections, and tuberculosis (2012−2016) is the current and third strategic plan for the fight against HIV infections [5]. The vision, goals and objectives, and core indicators of this strategic plan are shown in Box 1.

The vision is adapted from the "three zeros" on HIV, which is a 20-year vision by UNAIDS [5]. The goals and objectives were drafted based on evidence-based publications such as the "Know Your Epidemic" (KYE) report [19]. Each strategic objective has multiple subobjectives. Enablers that will ensure successful implementation of the strategic plan include: effective communication; good governance and functional institutional arrangements; research; and monitoring and evaluation using core indicators. Costing and financing are also factored into the strategic plan, with estimated annual cost of 1668.07 and 2872.34 billion US dollars in 2012/13 and 2016/17, respectively [5] (using an exchange rate of US 1$ = ZAR 11.2269).

Box 1
National strategic plan on HIV, sexually transmitted infections, and tuberculosis 2012 – 2016 in South Africa.

Vision:

- Zero new cases of HIV and TB infections.
- Zero vertical transmissions of HIV.
- Zero preventable mortality related to HIV and TB.
- Zero discrimination related to HIV, TB, and STIs.

Broad goals:

- Use combination of preventive measures to achieve at least 50% reduction in new HIV infection.
- Ensure that not less than 80% of eligible HIV-infected patients are started on antiretroviral treatment, with at least 70% of them alive and on the treatment five years following initiation of the therapy.
- Decrease the number deaths from TB and new cases of TB infection by 50%.
- Provide an accessible and enabling legal framework that promotes and protects the human right required to support successful implementation of the national strategic plan.
- Ensure that the self-reported stigma associated with TB and HIV is reduced by at least 50%.

Strategic objectives:

- Deal with the structural and social barriers related to HIV, TB, and STI care, prevention, and impact.
- Prevent new TB, HIV, and STI infections.
- Maintain wellness and health.
- Enhance access to justice and improve human rights protection.

Core indicators:

- Percentage of HIV-positive young men and women aged 15–24 years.
- Percentage of HIV-positive people in key populations such as sex workers, etc.
- Percentage and number of infants exposed to HIV whose HIV test is positive at six weeks and 18 months of ages.
- Incidence and prevalence of TB.
- Adult mortality percentage attributable to TB and HIV.
- Patterns of stigma.
- Retention of patients on ART.

Abbreviations: TB, tuberculosis; STI, sexually transmitted infections; ART, antiretroviral therapy.

The implementation of the strategic plan at every sector of the country is based on the following principles: (1) all initiatives should be vision led; (2) initiatives should be scalable and of high impact; (3) activities should be evidence based; (4) the strategic plans should be flexible to accommodate necessary changes; (5) multisectoral teamwork that considers local practices is required for success; (6) through partnership, the strategic plan should be promoted as having country ownership by all individuals; and (7) the national strategic plan should be rights based, ensuring human rights and gender equity [5].

In addition, important determinants of HIV infection were addressed in the strategic plan. Social and behavioral determinants include sexual debut, having multiple sexual partners, condom use, age-disparate coital relationships, substance and alcohol abuse, and knowledge of risk perception. The biological determinants include MTCT, medical male circumcision, prevention of different sexually transmitted infections, and initiating treatment on eligible HIV-positive patients as a preventive measure. Structural determinants are issues of mobility and migration, norms and gender roles, and intimate partner violence/sexual abuse. Further information on South Africa's national strategic plan on HIV is free to view online [5].

The first evaluation of South Africa's PMTCT program occurred in 2010 and a 3.5% rate of MTCT was reported [20]. The national strategic plan on HIV has identified a need for a strategic plan on HIV for sex workers [21]. In 2013, this then led to the development of a strategic plan entitled the "National Strategic Plan for HIV Prevention, Care and Treatment for Sex Workers" [21]. It is important to note that a review of the HIV, tuberculosis, and PMTCT programs in South Africa was carried out in 2013 and was reported in 2014 [22]. This was aimed to assess the performance of different programs and suggest measures for improvement. The review showed that MTCT based on positive PCR at eight weeks of age decreased to 2.6%/2.7% in 2011/2012 respectively [22].

5. Challenges associated with the South African 2013 PMTCT guidelines

In South Africa there are factors that occasionally prevent the complete implementation of the PMTCT guidelines, and as a result increase the risk of MTCT. These factors include booking for prenatal care at a late gestation, no monitoring of maternal viral load, failure to perform an HIV test on exposed infants, and inadequate ARV prophylaxis [16]. Others factors include poor quality data collection and management, failure to obtain any prenatal care, and inability to initiate ARVs at every public healthcare facility in the country [6]. In addition, overcrowding of maternity units predispose mothers to HIV transmission [23]. Gender-based violence and inadequate staffing of health facilities are also issues of concern.

There are measures that may be valuable in addressing the aforementioned challenges in South Africa. For instance, intensification of community health promotion will encourage citizens to avoid risky practices. The newly introduced "MomConnect" mobile phone text message services used to provide healthcare information to pregnant women will also be valuable [24]. Ongoing in-service training of medical staff will improve data management and adherence to the PMTCT guidelines. It is envisaged that the rollout of the national health insurance scheme [25] will provide the infrastructure and human resources required to promote health, as well as zero MTCT.

6. Conclusion

In South Africa, new drug regimens and the strategic plan on HIV have resulted in improved health outcomes such as a reduction in MTCT of HIV. This has been a major achievement. If the current challenges associated with implementation of the PMTCT guidelines are tackled and treatment option B+ adopted, it is hoped that complete elimination of MTCT will be a reality. Confidential enquiry into each

case of MTCT should be undertaken to identify and address gaps militating against complete elimination of vertical transmission.

Conflict of interest

The authors have no conflicts of interest.

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